

### Remarks

Applicants wish to thank the Examiner for the indication of allowability of claims 3, 5, 6, 24 and 25. Claims 1-25, 31, 32 and 53 remain before the Examiner and claims 26-30 and 33-52 have been withdrawn from consideration. Applicants added claim 54 which corresponds to previously presented claim 17. Claim 54 addresses what would have been an issue with improper dependency.

Please cancel claims 1, and 2.

#### **§112, Second Paragraph**

The Office rejected claims 31, 32, and 53 under 35 U.S.C. §112, second paragraph, and cited several reasons in support thereof. Applicants respectfully traverse the rejections.

In claims 31 and 32, the phrase "wherein the P1 amino acid residue" finds adequate antecedent basis because the P1 amino acid residue (Glutamic Acid-Glu) is inherently present at the Glu<sup>373</sup> – Ala<sup>374</sup> bond. The specification defines "P1" at page 14, line 18-24, and describes that the P1 amino acid is the amino acid on the N-terminal side of the sissel bond cleaved in the claimed substrate. One of ordinary skill in the art would have understood that the peptide of claim 3, 4, or 5 contained a P1 amino acid. The instant situation is akin to the scenario described in MPEP 2173.05 (e):

Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. >See *Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359, 61 USPQ2d 1216, 1218-19 (Fed. Cir 2001) (holding that recitation of "an ellipse" provided antecedent basis for "an ellipse having a major diameter" because "[t]here can be no dispute that mathematically an inherent characteristic of an ellipse is a major diameter").

Similarly, the phrase “ADMP-sensitive Glu<sup>373</sup>-Ala<sup>374</sup> bond” is definite. The numbering of the amino acid residues (373 for Glutamic acid and 374 for Alanine) provides a specific description of the residues in the claimed aggrecan fragments. The Glu<sup>373</sup>-Ala<sup>374</sup> residues, and the bond therebetween are in both SEQ ID NOs: 1 and 2. The numbering of the residues corresponds to the numbering of aggrecan residues (see *e.g.*, page 2, lines 28-31). Such enumeration is a routine practice in the art. It is clear that the bond recited in the phrase “ADMP-sensitive Glu<sup>373</sup>-Ala<sup>374</sup> bond” is the bond between the Glutamic acid at position 373 and the Alanine at position 374. In view of the foregoing, Applicants respectfully submit that claims 31 and 32 are clear and definite and that the rejection under §112, second paragraph should be withdrawn.

Regarding claim 53, the same general principles described above with respect to claims 31 and 32 apply. That is, the phrase “wherein said numbering” has proper antecedent basis because immediately preceding that phrase is a string of numbered amino acids corresponding to the human aggrecan protein. The inclusion of the numbers of the amino acid pairs identifying the site of ADMP cleavage renders the claim clear. With respect to a sequence identifier, Applicants submit that the plain language of claim 53 and the specific recitation of the ADMP cleavage site(s) in an isolated aggrecan peptide fragment clearly identifies the metes and bounds of the claimed invention and that a sequence identifier is not necessary.

In view of the foregoing, favorable consideration is respectfully requested.

#### **§112 First Paragraph – Written Description**

The Office maintains that claims 1, 2, 8-23, 31, 32, and 53 are not adequately described in the specification under §112, first paragraph (written description). Applicants respectfully traverse the Office’s position.

The Office relies heavily on the *Lilly* case and maintains that Applicants' specification does not provide sufficient structural description to entitle Applicants to the claimed subject matter. Applicants submit that 1) *Lilly* is distinguishable and has been clarified in subsequent case law; and 2) the full scope of the claims is adequately described.

Contrary to the position of the Office, Applicants' claims indeed recite common structural features—an ADMP specific susceptible cleavage site. All embodiments of the claims share such cleavage sites in common. In many instances in the specification, there are specific cleavage sites described (*e.g.*, Glu<sup>373</sup>-Ala<sup>374</sup>, Glu<sup>1545</sup>-Gly<sup>1546</sup>, Glu<sup>1714</sup>-Gly<sup>1715</sup>, Glu<sup>1819</sup>-Ala<sup>1820</sup>, Glu<sup>1919</sup>-Leu<sup>1920</sup>; *see* page 6, line 37 – page 7, line 6). Such disclosure provides the exact location of exemplary cleavage sites. These specific disclosures are also embodied in the sequence listings. The multiple species described are representative of the claimed subject matter and would have been sufficient to have allowed one of ordinary skill in the art to predict other species having ADMP-susceptible cleavage sites.

Moreover, *Lilly* is readily distinguishable from the facts in the instant case. In *Lilly* the issue essentially was whether the term “cDNA” in the context of previously undescribed and unknown DNA sequences, carried any descriptive weight for claims to *human* insulin cDNA. In the instant case, the term “aggrecan” is recited in the claims, which would have readily conveyed ample distinguishing information to those skilled in the art at the time of filing. Applicants note that case law subsequent to *Lilly* (*See e.g., Amgen Inc., v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003)), found that the words “vertebrate” and “mammalian” were sufficient to describe exactly what types of cells were at issue in that case. (Applicants also note that only two specific examples of cell types used to express erythropoietin were provided in *Amgen*; contrast that with multiple examples described by Applicants). The

instant case is factually similar to *Amgen* insofar as the inclusion of “aggrecan” and “fragment” in the claims would have conveyed exactly the nature of the claimed subject matter just as the terms “mammalian” and “vertebrate” in *Amgen*. The former terms are clearly described in Applicants’ specification and thus the claims should found to comply with §112, first paragraph. Favorable consideration is requested.

### **§112 First Paragraph – Enablement**

The Office maintains that claims 1, 2, 7-23, 31, 32, and 53 are not adequately enabled by the specification under §112, first paragraph. In addition to those claims listed at point number 13 on page 5 of the February 2006 action, it appears that the Office intended to reject claim 4. Applicants will move forward under that assumption. Applicants respectfully traverse the Office’s position.

The Office maintains that the claims encompass “...any peptide or peptide fragment or any function...” (see page 5, Feb. 2006 Office Action). Applicants respectfully submit that position is not accurate. The claims as amended recite isolated aggrecan fragments comprising an ADMP-susceptible cleavage site. The language of the claims reflect that the claims differ in scope than that maintained by the Office, and, as such, the properly interpreted claims are adequately enabled by the specification.

On page 5, third paragraph under point 13., the Office appears to suggest that the utility of the claimed fragments is in question:

However, knowledge regarding the biological utility of the claimed peptides and the specific amino acid residues to change without affecting biological activity of the claimed peptides or peptide fragment is lacking.

Applicants respectfully submit that the utility of the claimed subject matter is clear, and is a distinct inquiry from the enablement inquiry. The enablement inquiry is a question of law

based on underlying fact. The utility of Applicants' invention is clear and the facts lead to the legal conclusion that the amount of experimentation to practice the full scope of the rejected claims would not have been "undue." For example, amended claim 4 recites:

An isolated aggrecan peptide fragment consisting of a sequence of amino acids that is at least 80% identical to the sequence consisting of amino acids 1-40 of SEQ ID NO:1

Claim 4 clearly defines the metes and bounds such that one of ordinary skill in the art could have looked to Applicants' specification, and employed his/her knowledge, to obtain a peptide fragment of claim 4, without resorting to 'undue' experimentation. The 'reference' point of amino acids 1-40 of SEQ ID NO:1 is fixed. The percent identity to the amino acid sequence is also fixed. One of ordinary skill in the art at the time the application was filed could have readily designed and synthesized sequences having the claimed percent identity to SEQ ID NO:1, and evaluated the activity of the peptides by following the disclosure provided in Applicants' specification (see *e.g.*, Examples 1 and 2). The claim recites specific identity parameters and the specification provides a substantial amount of guidance for evaluating the activity of the peptides themselves.

Applicants respectfully disagree with the Office's position that the amount of experimentation required would be "enormous and undue." As described above, the source of peptides would be an aggrecan, and would not entail "searching a vast number of biological sources from which to isolate the peptide or peptide fragment...". The peptides themselves can be made commercially (*see* page 15, lines 30-37). Moreover, eighty percent identity of the forty residues of SEQ ID NO:1 reflects that the claimed fragments must share at least 32 out of 40 amino acids of SEQ ID NO:1. There is no evidence of record that suggests synthesis of such fragments, followed by assay of their activity as clearly described in the specification rises to the

level of “undue” experimentation. Applicants submit that by following the disclosure in the specification, a sufficient number of operative embodiments of the claimed invention would be obtained following only routine experimentation. The peptides could then be assayed for activity using the methods described in the application. Applicants specification provides a substantial amount of guidance and direction for practicing the claimed subject matter. Therefore, Applicants submit that the rejection under §112, first paragraph-enablement should be withdrawn. Favorable consideration is respectfully requested.

**§102 – Fosang, Genbank NP\_037359 and 00126, Doege and Antonsson**

The Office rejected a number of claims under §102 in view of a number of references. Applicants respectfully traverse each rejection for the reasons set forth below.

As noted above, claims 1 and 2 have been canceled and claims 15 and 16 have been amended to recite dependency on any one of claims 3-7.

The Office rejected claim 4 in view of Doege, and claim 7 in view of Antonsson. Applicants note that the September 1999 reference relied upon by the Office is not prior art to claim 4. Applicants maintain that the application is entitled to priority to each of several earlier-filed applications, the earliest of which was filed on July 25, 1997. Applicants note that claims 4 and 7 have been amended to recite “An isolated aggrecan peptide fragment ‘consisting of’ a sequence...”. Applicants submit that the claims are in condition for allowance. Favorable consideration is respectfully requested.

**§103 – Fosang and Koristas; Fosand, Koristas & Duan**

The Office rejected a number of claims under §103 in view of a number of references. Applicants respectfully traverse each rejection for the reasons set forth below.

Applicants submit that the amendments submitted herewith render moot the previously maintained §103 rejections. For example, claim 2 has been canceled, claim 8 has been amended to recite dependency on any one of claims 3, 4, 5, 6, or 7, claims 9-14 have been amended to recite dependency on claim 8, and claims 17-21 have been amended to recite different dependency.

Regarding claims 31 and 32, the Office maintains that “Furthermore, it would have been within the purview of one of ordinary skill in the art to esterify of [sic] replace the P1 amino acid Glu as recited in claims 31 and 32 in order to prevent proteolytic hydrolysis of the substrate peptide.” (see page 8, penultimate paragraph).

Applicants respectfully submit that whether a particular technique is within the “purview” of one of ordinary skill in the art is essentially irrelevant to an inquiry under §103. The proper inquiry is whether there would have been sufficient motivation to esterify or replace the P1 amino acid as recited in the claims. The Office fails to cite any references or evidence that provides the requisite *prima facie* evidence to show that one of ordinary skill in the art would have been motivated to combine reference(s) and/or knowledge in the art, to obtain the subject matter recited in claims 31 and 32. The art must lead to the claimed subject matter and not the converse. That is, using the claims as a tool to frame what was known in the art is an improper use of hindsight for purposes of analyzing patentability of claims under §103.

Similarly, it appears that the Office has applied impermissible hindsight in rejecting claims 10, 22, and 23. The existence of an available technique that *might* be used to obtain claimed subject matter (*e.g.*, Duan) is insufficient to establish a *prima facie* case of obviousness. There must be some teaching or suggestion in the cited reference, or evidence that such information was known by those of ordinary skill in the art, that establishes the requisite

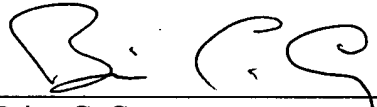
motivation to combine the references. Based on the teaching of Fosang, there would not have been motivation to expand upon the teaching present in Fosang and take the additional steps recited in claims 10, 22 and 23. Absent such motivation, the Office's position with respect to the patentability of claims 10, 22, and 23 should be withdrawn.

Based on the foregoing, Applicants respectfully submit that the claims are patentable and in condition for allowance.

No fee is deemed necessary by applicants in connection with this filing, other than the fee required in connection with the accompanying petition. However, if any other fee is required, authorization is hereby given to charge the amount to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

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Respectfully submitted,

  
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